REMARKS

Claims 1-34 are pending in this application with Claims 7-34 having been withdrawn from consideration by the Examiner. Claims 1, 4, and 5 have been amended. In particular, Claim 1 has been amended to indicate that the level of nitric oxide is reduced sufficiently enough by the nitric oxide synthase inhibitor(s) to inhibit zinc release from the neurons. Claim 4 is amended to remove a duplicate entry of the nitric oxide synthase inhibitor agent, N(6)-iminoethyl-L-lysine. Claim 5 is amended to incorporate the limitation of reducing zinc-mediated brain injury by inhibition of zinc release, and is supported by the specification (page 42, lines 13-19 and Figures 9A-9B). No new matter is added.

The Drawing Objection per 37 CFR 1.121(d)

The drawings filed on March 22, 2004, and on July 27, 2004, are objected to because the copies are too dark for Figures 2A, 4A-4F, 6 and 10A-10D, which prevents their proper interpretation by the Examiner.

Applicant submits drawing replacement sheets per 37 CFR 1.121(d) for Figures 2A-2B, 4A-4F, 5-6, and 10A-10D.

Applicant has adjusted the drawings to increase the light and tissue detail. Applicant notes that the top left image in Figure 6, captures a baseline measurement image of fluorescent Zn^{2+} that has been released into the hippocampal extracellular fluid. This particular image is normally low as stated in the brief description of the drawings (page 16, line 16). This image should be compared to the upper and lower right-hand images in Figure 6, whereby fluorescent Zn^{2+} in the extracellular hippocampal fluid is readily detected and apparent after the hippocampal tissue releases fluorescent Zn^{2+} once exposed to the nitric oxide generator, S-nitroso-N-acetyl-L-penicillamine (SNAP). In view of the submission of replacement sheets per 37 CFR 1.121(d) for Figures 2A-2B, 4A-4F, 5-6 and 10A-10D, Applicant requests that the objection to the drawings be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1, and 5-6 are rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification is enabling for treating a zinc-mediated brain injury by inhibiting zinc release but does not reasonably provide enablement for preventing a zinc-mediated brain injury. Applicant respectfully traverses this rejection.

Claims 1 is drawn to a method of inhibiting zinc release from neurons by inhibiting nitric oxide synthesis in neurons, and Claim 5 has been amended to recite that the inhibition of zinc release reduces zinc-mediated brain injury, thereby rendering this rejection moot. In particular, it is submitted that none of the pending claims are directed to preventing a zinc-mediated brain injury. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §102 rejection

Claims 1-6 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Montécot et al., *Neuroscience*, **1998**, *84*(3), pp 791-800 (the "Montécot et al. reference"). In particular, the Office Action alleges that the basis for this rejection is "that the instant claims entail only the step of administering an agent, e.g., 7-nitroindazole, to inhibit nitric oxide synthase in neurons." See page 7 of the Office Action.

Without commenting on the merits of this rejection, Claim 1 has been amended to indicate that the reduction of nitric oxide level need to be sufficient enough to inhibit release of zinc from the neurons. Accordingly, pending claims entail more than the step of administering a nitric oxide synthase inhibitor. In particular, pending claims require that a sufficient amount of at least one agent that inhibits nitric oxide synthesis be administered to inhibit release of zinc from the neurons.

As will be recognized, claims are anticipated if, and only if, **each and every element** as set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1989). Furthermore, "[t]he **identical invention must be shown in as complete detail as is contained in the...claim**." (emphasis added) *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913 (Fed. Cir. 1989). See also, *PPG Industries Inc. v. Guardian Industries Corp.*, 7 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.").

Applicant respectfully submits that the Montécot et al. reference does not teach or describes a method of inhibiting zinc release from neurons by inhibiting nitric oxide synthesis in neurons. More significantly, it appears the Montécot et al. reference does not recognize or even mention release of zinc by neurons. In contrast, the Montécot et al. reference appears to be using

a nitric oxide synthase inhibitor as a means for controlling cerebral blood flow. Specifically, the Montécot et al. reference states:

> NO has also been proposed to mediate glutamate toxicity, as excessive stimulation of NMDA receptors increases the NO concentration to toxic levels. However, the toxicity of h O seems to originate more in its reaction with oxygen-related compounds than in its direct effect.
>
> In the present study, we investigated the possible roles of NO released from neurons during status epilepticus. All investigations were performed in the hippocampus, since this structure plays a paramount role in kainate-induced seizure. **The aim of the study was to determine the involvement of neuronally derived NO in the regulation of local blood flow, tissue oxygenation and neuronal damage triggered by status epilepticus, and to analyse any relationships between these events**.

(Emphasis added). See the Montécot et al. reference at p. 792, left column, paragraphs just prior to the "Experimental Procedures" section. Accordingly, methods discussed by the Montécot et al. reference are directed to "regulation of local blood flow, tissue oxygenation and neuronal damage…" and analysis of relationships between these events.

Since **every element** as set forth in the claim is **not** found in the Montécot et al. reference, 35 U.S.C. § 102(b) rejection based on the Montécot et al. reference is improper and contrary to the Court's holding in *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1989). Accordingly, it is respectfully requested that the rejection under 35 U.S.C. § 102(b) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 1-6 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Frederickson, *International Review of Neurobiology*, **1989**, *31*, pages 145-238 (the "Frederickson reference"), in view of the teachings of Bagetta et al., *Biochemical and Biophysical Research Communications*, **2002**, *291*, pages 255-260 (the "Bagetta et al. reference"), and Suh et al., *Brain Research*, **2001**, *895*, pages 25-32 (the "Suh et al. reference").

Broadly, the Office Action appears to be stating that: (1) the Frederickson reference teaches that zinc plays a role in epilepsy and CNS zinc levels are abnormal in patients and animals suffering from seizures; (2) the Bagetta et al. reference teaches tacrine-induced seizures induce nNOS expression and pretreatment with an nNOS inhibitor prevents seizures and neuronal cell death; and (3) the Suh et al. reference teaches that chelatable zinc release is involved in seizure-induced neuronal death.

However, the Office Action acknowledges that the Frederickson reference does not teach the involvement of nitric oxide synthase in seizures and chelating zinc to treat seizures. See page 8 of the Office Action.

But the Office Action alleges that "it would have been obvious to a person of skill in the art at the time of the invention to employ the teachings of Frederickson to treat epilepsy seizures because the compounds of Bagetta et al. are the inhibitor of nNOS…." See page 9 of the Office Action.

The Office Action also alleges that "it would have been obvious to a person of skill in the art at the time of the invention to employ the teachings of Frederickson to treat epilepsy or seizures because the compounds of Suh et al. are chelatable zinc and according to Suh et al., chelated zinc treats epilepsy and seizures." *Id.*

As an initial matter it is noted that it is well established law that in order to establish a *prima facie* case of obviousness, the Examiner must provide a sufficient evidence showing that either the cited reference(s) or the knowledge generally available to one of ordinary skilled in the art provides some suggestion or motivation to modify or combine reference teachings. See MPEP §2145(X)(c). As discussed in detail below, it is submitted that the Office Action does not provide any evidence showing necessary motivation or suggestion to modify or combine the reference teachings.

In contrast to the assertion in the Office Action, the Frederickson reference teaches that zinc has no clear role in seizure pathophysiology. In particular, the Frederickson reference states:

> The foregoing encourages the general notion of a zinc role in seizure pathophyiology, but closer view of the evidence does not lead to any simple, unitary hypothesis about the underlying mechanisms. For example, whereas mice genetically prone to seizures have elevated brain zinc…, genetically seizure-prone rats have 47% less zinc in the hippocampal mossy fiber region than control rats…. Similarly, zinc in the serum of seizure-prone baboons…is apparently elevated…, whereas the CSF of children undergoing "fifth-day fits"…, and the serum of preeclamptic women…are characterized by subnormal zinc concentration. In adult patients suffering from epileptic disorders, some investigators have found changes in serum zinc…, but other evidence indicates that neither epilepsy nor anticonvulsant drug therapy is consistently associated with any abnormalities of serum zinc…. These findings suggest that the amount of zinc in the brain, CSF, and serum may vary depending on the eitology [sic], clinical history, and status of seizure-prone individuals or populations. Oral zinc supplements have been used as a therapy for Wilson's disease to lower the copper levels in those patients. Despite two-fold increases in serum zinc, no seizure disorders have been reported….

Page 217 of the Frederickson reference. Accordingly, the Frederickson suggests that zinc levels in brain vary depending on individual or population investigated. Zinc ions can produce

proconvulsive and anticonvulsive changes at the synaptic level and "**which of those that would predominate…would be impossible to predict** from the available data." (Emphasis added). (Page 218 of the Frederickson reference, 4th paragraph).

Without commenting on the merits of the assertion in the Office Action regarding the Bagetta et al. reference and the Suh et al. reference and assuming accuracy of the characterization of these references (however, Applicant reserves the right to challenge the merits and accuracy of such characterization), at best the Bagetta et al. reference teaches tacrine-induced seizures induce nNOS expression and pretreatment with an nNOS inhibitor prevents seizures and neuronal cell death; and the Suh et al. reference discusses that chelatable zinc release is involved in seizure-induced neuronal death.

At the very best, the Bagetta et al. reference provides a link between seizure and expression of nNOS. Nothing in the Frederickson reference or the Bagetta et al. reference teaches, suggests, discusses, or even hints at any link between zinc and nitric oxide.

As for the Suh et al. reference, at the very best it discusses a possible link between zinc and seizure. However, the Suh et al. reference, like that of the Frederickson reference and the Bagetta et al. reference does not teaches, suggests, discusses, or even hints at any link between zinc and nitric oxide.

In fact, none of the cited references either alone or in combination teach, suggest or even remotely discuss methods for inhibiting zinc release in neurons by reducing nitric oxide level in the neurons.

More significantly, the primary reference relied upon in the Office Action for the 35 U.S.C. §103(a) rejection, i.e., the Frederickson reference, explicitly states that "…the amount of zinc in the brain, CSF, and serum may vary depending on the eitology [sic], clinical history, and status of seizure-prone individuals or populations..." (page 217 of the Frederickson reference) and that the influence of zinc ions "would be impossible to predict from the available data." Page 218 of the Frederickson reference. Such statements in the Frederickson reference would discourage one skilled in the art from drawing a conclusion that there is a link between seizure and the zinc level.

In view of the above, it is clear that there is no teaching or motivation to combine the cited reference in a manner suggested in the Office Action. More significantly, even if the

references were combined, and the Applicant maintains there is no teaching or motivation to do so, the combination would not lead to the invention of the pending claims. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. §103(a) be withdrawn.

Double Patenting Rejection

Claims 1 and 5-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over Claims 25, 39, 41, 51, 56, and 60 of copending Application No. 10/929,924.

It is respectfully requested that this matter be deferred until an allowable subject matter has been indicated by the Examiner.

CONCLUSION

In view of the foregoing, Applicants submit that all claims now pending in this Application are in condition for allowance. Therefore, an early Office Action to that effect is earnestly solicited. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at (303) 955-8103.

Respectfully submitted,

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Date: January 28, 2008

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